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(54) Method of producing amorphous paroxetine hydrochloride

(57) A method of producing amorphous paroxetine hydrochloride, which comprises converting paroxetine or its lower alkanoic acid salt into paroxetine hydrochloride and then spray drying a solution of the hydrochloride.

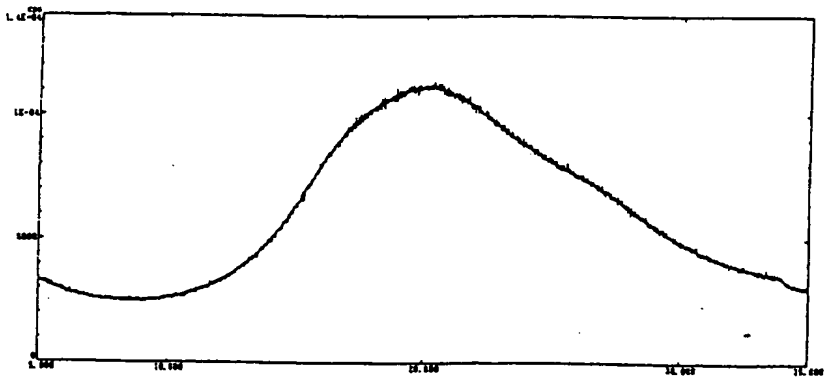

FIGURE 1

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Description

The present invention relates to a method of producing paroxetine hydrochloride which has an inhibitory action on 5-hydroxytryptamine (5-HT) and is useful as a therapeutic agent for various diseases such as depression and Parkinson's diseases.

Paroxetine hydrochloride, i.e. (3S,4R)-3-[5-(1,3-dioxaindanyl)oxymethyl]1-4-(p-fluorophenyl)piperidine hydrochloride, has been obtainable in the crystalline form, and hemihydrated paroxetine hydrochloride is also known in the crystalline form (U.S.P No. 4,007,196, and Japanese Examined Patent Publication JP-B-6-47587). However, because of their crystallinity, they are medicines which are slowly absorbed into the body.

To solve the problem, the present invention provides a method of producing amorphous paroxetine hydrochloride which is generally easy to absorb.

Namely, the present invention provides a method of producing amorphous paroxetine hydrochloride, which comprises converting paroxetine or its lower alkanoic acid salt into paroxetine hydrochloride, and then spray drying a solution of the hydrochloride.

Figure 1 is the X-ray powder diffraction pattern of the amorphous paroxetine hydrochloride.

Paroxetine is obtainable by the method disclosed in U.S.P. 4,007,196 and the like. A lower alkanoic acid salt of paroxetine can be obtained easily by mixing paroxetine with the corresponding lower alkanoic acid.

In the present invention, "lower" means a carbon number of at most 6. As the lower alkanoic acid, an alkanoic acid having a carbon number of at most 4 is preferred, and the most preferred is acetic acid.

In the method of the present invention, it is preferred to dissolve paroxetine or its alkanoic acid salt in an appropriate solvent, and then add a solution of hydrogen chloride in an appropriate solvent or directly introduce gaseous hydrogen chloride to the resulting paroxetine solution to prepare a solution of paroxetine hydrochloride. The amount of hydrogen chloride to be used is preferably at least equivalent to the used paroxetine or its salt. The reaction temperature is preferably from -20 to +50°C, more preferably from -10 to +30°C.

The solvent to be used is in general a solvent which dissolves amines and their salts, and preferably a saturated alcohol having a boiling point of at most 170°C, or water. Particularly preferred are lower saturated alcohols such as methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, 2-methyl-1-propanol and 2-methyl-2-propanol. The most preferred solvent is ethanol.

Then, the resulting solution of paroxetine hydrochloride is concentrated in vacuo to remove the substances other than paroxetine hydrochloride in the system upon evaporation. When a saturated alcohol is used as the solvent, the lower alkanoic acid in the system is removed in the form of an ester.

The resulting residue is already amorphous at this time, but an amorphous substance like this is usually so hygroscopic that it is usually hard to handle. Powdery amorphous paroxetine hydrochloride which is easy to handle can be obtained by dissolving the residue in an appropriate solvent and spray drying the paroxetine hydrochloride solution.

The solvent to be used in this step may be any solvent which dissolves paroxetine hydrochloride, and, preferably has a boiling point at most 120°C. For example, toluene, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, methanol, ethanol, 2-propanol, 2-methyl-2-propanol, water or a mixture thereof may be mentioned. Particularly preferred are lower alcohols, and the most preferred solvent is ethanol.

When a lower saturated alcohol such as ethanol is used as the solvent in the above step to prepare a paroxetine hydrochloride solution from paroxetine or its alkanoic acid salt, the resulting paroxetine hydrochloride solution can be directly spray dried without concentration to obtain amorphous paroxetine hydrochloride. When a lower alkanoic acid salt of paroxetine is used as the starting material, the lower alkanoic acid generated upon salt exchange reaction and ethanol as the solvent form an ester having a lower boiling point, which can be readily removed by spray drying.

In general the apparatus and condition for spray drying may be the same as those used for producing amorphous medicines or food. In the case of a non-aqueous solvent, a spray drying apparatus which can recover the solvent is preferred. The feed stock solution may be used in any concentrations so long as it is not saturated. When a good flowability is required, a dilute feed stock solution is preferred.

The particle size of the resulting amorphous powder can be controlled by changing the concentration of the feed stock solution, the size of the spray nozzle or the feed rate. The feed rate depends on the capacity of the apparatus but is preferred to be controlled according to the particle size or the dryness of the resulting powder. The inlet temperature of the chamber of the apparatus is preferably set within a range of from 30 to 200°C, depending on the boiling point of the solvent and the dryness, more preferably within a range of from 40 to 160°C. As the powder obtained by spray drying is usually charged with static electricity, it is preferred to earth the powder receiver to eliminate static electricity.

In the above mentioned steps, by forming and spray drying the hydrochloride virtually in the absence of water, it is possible to obtain the hydrochloride in the anhydrous form. The amorphous paroxetine hydrochloride of the present invention is preferably an anhydride obtained virtually in the absence of water.

The amorphous paroxetine hydrochloride of the present invention is a powder which substantially contains no crystals. Figure 1 is the X-ray powder diffraction pattern of the amorphous paroxetine hydrochloride obtained by spray drying. It clearly indicates the halo effect, and the quite low intensity suggests an amorphous pattern. In contrast, the X-ray powder diffraction pattern of crystals of the hemihydrate paroxetine hydro-

chloride disclosed in Japanese Examined Patent Publication JP-B-6-47587 (Figure 1 in the publication) shows a clear peak.

Now, the present invention will be described in further detail with reference to Examples. However, it should be understood that the present invention is by no means restricted to such specific examples.

EXAMPLE 1

1.51g of paroxetine was dissolved in 30 ml of ethanol, and 3 ml of a 22 wt% solution of hydrogen chloride in ethanol was added under cooling with ice. The resulting solution was left to stand at room temperature for an hour to obtain a solution of paroxetine hydrochloride in ethanol.

The solution of paroxetine hydrochloride in ethanol was spray dried by a spray drying machine for organic solvents (type: GS31, manufactured by Yamato Scientific Corporation) under the conditions of the nozzle size: 0.4 mmØ, the feed rate: 11.7 g/min and the inlet temperature: 90°C, to obtain 1.2g of anhydrous amorphous paroxetine hydrochloride.

^{1}H NMR(400MHz,$CDCl_3$) δ 9.9(br,2H);7.20-7.23(m,2H); 6.98-7.02(m,2H);6.62(d,J=8.4Hz,1H);6.34(d,J=2.2Hz,1H); 6.12(dd,J=2.2,8.4Hz,1H);5.89(s,2H);3.73(br,1H);3.67 (br,1H);3.60(m,1H);3.48(m,1H);3.17(br,1H);3.05(br,1H) ; 2.92(br,1H);2.66(br,1H);2.40(br,1H);2.04(br,1H).

^{19}F NMR(376MHz,$CDCl_3$,$CFCl_3$=0ppm) δ -115.4.

Figure 1 is the X-ray powder diffraction pattern of the amorphous paroxetine hydrochloride obtained by the following instrument.

Instrument: Rotorflex RU-200, manufactured by Rigaku Denki Company Limited

Measuring conditions:

Tube target: Cu, Tube voltage; 50 kV, Tube current; 200 mA,
Sampling width; 0.010°, Scanning rate; 0.500°/minute,
Scanning axis; 2θ/θ, Divergent slit; 1°, Scattering slit; 1°,
Receiving slit; 0.30 mm.

EXAMPLE 2

13.9g of paroxetine was dissolved in 100 ml of ethanol, and 10 ml of a 22 wt% solution of hydrogen chloride in ethanol was added to obtain a solution of paroxetine hydrochloride in ethanol. The solution of paroxetine hydrochloride in ethanol was concentrated in vacuo, and 3.2g of the residue was dissolved in 100 ml of ethanol. This solution was spray dried with the same machine under the same conditions as in Example 1 to obtain 2.3g of anhydrous amorphous paroxetine hydrochloride.

^{1}H NMR(400MHz,DMSO-d_6) δ 8.80(br,2H);7.22-7.25(m,2H); 7.14-7.19(m,2H);6.74(d,J=8.4Hz,1H); 6.49(d,J=2.4Hz,1H); 6.19(dd,J=8.4Hz,2.4Hz,1H); 5.93(s,2H);3.59(m,1H);3.49 (m,2H);3.42(m,1H);2.97(m, 2H);2.86(m,1H);2.67(br,1H);1.97 (m,1H);1.90(m,1H).

^{19}F NMR(376MHz,DMSO-d_6,$CFCl_3$=0ppm) δ -116.01.

EXAMPLE 3

9.8g of paroxetine acetate was dissolved in 80 ml of ethanol, and then 12 ml of a 22 wt% solution of hydrogen chloride in ethanol was added to obtain a solution of paroxetine hydrochloride in ethanol. 40 ml of the solution of paroxetine hydrochloride in ethanol was spray dried with the same machine under the same conditions as in Example 1 to obtain 3.5g of anhydrous amorphous paroxetine hydrochloride.

EXAMPLE 4

40 ml of the solution of paroxetine hydrochloride in ethanol obtained in Example 3 was concentrated in vacuo, and the residue was dissolved in 60 ml of ethanol. This solution was spray dried with the same machine under the same conditions as in Example 1 to obtain 3.1g of anhydrous amorphous paroxetine hydrochloride.

EXAMPLE 5

10.5g of paroxetine was dissolved in 950 ml of water, and 11 ml of 3N hydrochloric acid was added under cooling with ice to obtain an aqueous solution of paroxetine hydrochloride. The aqueous solution of paroxetine hydrochloride was spray dried by using a mini spray drier (type: GA32, manufactured by Yamato Scientific Corporation) under the conditions of the nozzle size: 0.4 mmØ, the feed rate: 9.4 g/min and the inlet temperature: 160°C, to obtain 7.8g of hydrous amorphous paroxetine hydrochloride.

EXAMPLE 6

1146g of paroxetine acetate was dissolved in 5.4L of ethanol, and then a solution of hydrogen chloride in ethanol (221g/1.6L) was added to obtain a solution of paroxetine hydrochloride in ethanol. This solution was concentrated in vacuo, and the residue was dissolved in 36L of ethanol.

The solution of paroxetine hydrochloride in ethanol was spray-dried by a spray drying machine for organic solvents (type: DA2SW-16, manufactured by Sakamoto Engineering CO., LTD.) under the conditions of the revolution of atomizer: 10,000 - 12,000 rpm, the feed rate: 3 - 4 L/hr and the inlet temperature: 110 - 130°C, the obtain 523.4g of anhydrous amorphous paroxetine hydrochloride.

It is possible to produce amorphous paroxetine

hydrochloride which is useful as a medicine.

Claims

1. A method of producing amorphous paroxetine hydrochloride, which comprises converting paroxetine or

   a lower alkanoic acid salt thereof into paroxetine hydrochloride and then spray drying a solution of the hydrochloride.

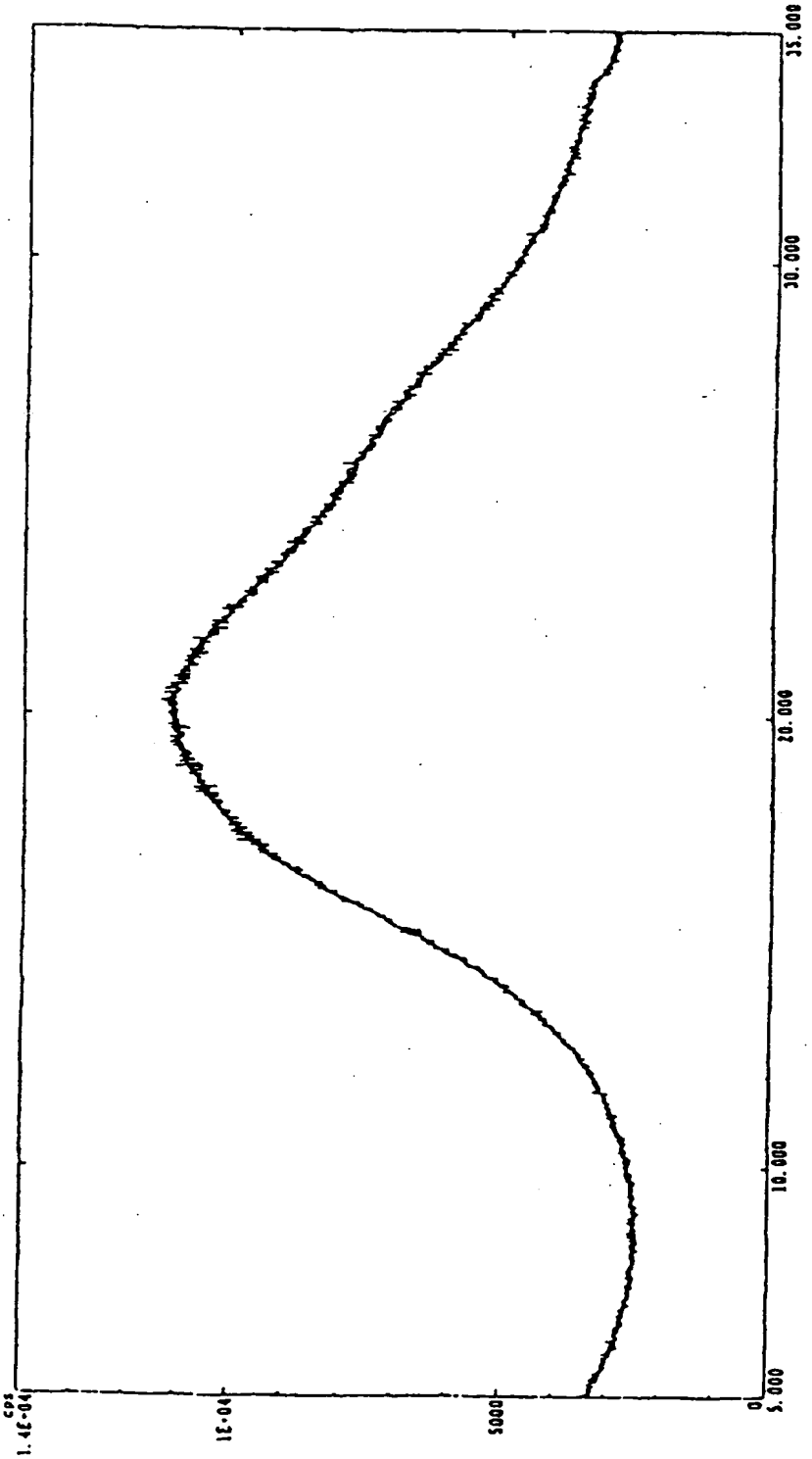
2. The method according to Claim 1, wherein paroxetine or a lower alkanoic acid salt thereof is converted into paroxetine hydrochloride in water or a saturated alcohol.

3. The method according to Claim 1, wherein paroxetine or a lower alkanoic acid salt thereof is converted into paroxetine hydrochloride in a lower saturated alcohol.

4. The method according to Claim 1 or 3, wherein paroxetine or a lower alkanoic acid salt thereof is converted into paroxetine hydrochloride in a lower saturated alcohol, and the resulting solution of paroxetine hydrochloride in the lower saturated alcohol is spray dried.

5. The method according to any one of Claims 1, 3 and 4, wherein anhydrous amorphous paroxetine hydrochloride is produced in the absence of water.

FIGURE 1



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EUROPEAN SEARCH REPORT

Application Number
EP 97 10 8713

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A,D	US-A-4 007 196 (CHRISTENSEN JORGEN ANDERS ET AL) 8 February 1977 * example 2 *	1-5	C07D405/12
A,D	EP-A-0 223 403 (BEECHAM GROUP PLC) 27 May 1987 * page 3 *	1-5	
A	WO-A-95 15155 (SMITHKLINE BEECHAM FARMA ;FRANCESE FRANCO (IT); MANESCHI MASSIMO () 8 June 1995 * claim 2 *	1-5	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

C07D
A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	14 August 1997	Frelon, D

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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